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Tetrahydroisoquinolines

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SPECIFICATION

Tetrahydroisoquinolines

5 In anesthesia, neuromuscular blocking agents are used to provide skeletal muscular relaxation during surgery and during intubation of the trachea. 5

In general there are two types of neuromuscular blocking agents in use, non-depolarizing and depolarizing.

10 The non-depolarizing agents include d-tubocurarine, pancuronium, gallamine, diallyltoxiferine and toxiferine. 10

The depolarizing agents include succinylcholine and decamethonium. All of the conventional non-depolarizing agents when used for producing skeletal muscle relaxation in surgery have a long duration of action, e.g. 60 to 180 minutes in man. The depolarizing agents, on the other hand, provide muscle relaxation 15 with duration of action shorter than that of the non-depolarizing agents. 15

For example, succinylcholine provides a short duration of action of about 5 to 15 minutes whereas decamethonium provides about 20 to 40 minutes duration of muscle relaxation in man.

The long duration of action of non-depolarizing agents is unacceptable in many surgical procedures which take less than one hour because the patient is not generally fully recovered from their effects, e.g. the patient 20 may be unable to breathe adequately on his or her own. 20

Each non-depolarizing agent has inherent side effects. For example, gallamine and pancuronium may cause tachycardia, and d-tubocurarine and diallyltoxiferine may cause hypotension.

While these drugs can be pharmacologically antagonized with anticholinesterase agents, this obviously necessitates the administration of a second drug which itself may have its own side effects e.g., bradycardia, 25 gut spasm and bronchospasm. Thus, to overcome the aforementioned side effects of the anticholinesterase agents, a third drug, an anticholinergic drug, e.g. atropine must also be given. 25

The depolarizing agents to the best of applicant's knowledge have no pharmacologic antagonists. While in most cases there is no need to reverse the effects of the depolarizing agents, in certain patients the effects of succinylcholine are much prolonged because of abnormal metabolism of the agent by the patient.

30 The depolarizing agents due to that mode of action which initially causes skeletal muscle contraction and stimulation of smooth muscles are also known to cause the following side effects in certain instances: 30 increased intraocular, and intragastric tension; cardiac arrhythmias, potassium release, and muscle pain.

These side effects caused by the depolarizing agents are not caused by the non-depolarizing agents. It is, therefore, clearly evident that a new neuromuscular blocking agent is needed which would combine the 35 short duration of action of the depolarizing agents with the relatively few side effects and the reversibility of the non-depolarizing agents. 35

It should be understood that while non-depolarizing agents generally have few side effects, gallamine and pancuronium may cause tachycardia and d-tubocurarine and diallyltoxiferine may cause hypotension.

Surprisingly, the compounds of the present invention appear to be free of these side effects at the dosages 40 anticipated being used clinically in tests made to date. Reference may be made to the text:

The Pharmacological Basis of Therapeutics-Fifth Edition, edited by Louis S. Goodman and Alfred Gilman published by The McMillian Co., copyright 1975, Chapter 28, author George B. Koelle, for further description 40 of neuromuscular blocking agents.

Reference should also be made to the following articles:

45 Neuromuscular Blocking Activity of a New Series of Quaternary N-Substituted Choline Esters - British Journal of Pharmacology, September, 1971, vol. 43, No. 1, p. 107. 45

The Pharmacology of New Short Acting Non-depolarizing Ester Neuromuscular Blocking Agents: Clinical Implications - published in Anaesthesia and Analgesia.... Current Researches, Vol. 52, No. 6, p. 982, Nov.-Dec., 1973.

50 Potential Clinical Uses of Short-Acting Non-depolarizing Neuromuscular-Blocking Agents as Predicted from Animal Experiments - published in Anaesthesia and Analgesia... Current Researches, Vol. 54, No. 5, p. 669, Sept.-Oct., 1974; and 50

U.S. Patent No. 3,491,099, for a further description of neuromuscular blocking agents.

U.S. patent 3,004,031 granted Oct. 10, 1961 discloses a group of substituted laudanosinium salts having 55 neuromuscular blocking activity with non-depolarizing properties. 55

Belgium patent 869,415 granted January 31, 1979 discloses a group of substituted tetrahydroisoquinolinium salts having neuromuscular blocking activity, with non-depolarizing properties and a short duration of action. Spanish Patent of Invention No. 477,257 granted April 25, 1979 [notice published in Spanish Official Gazette of August 1, 1979] discloses a second group of substituted tetrahydroisoquinolinium salts having 60 neuromuscular blocking activity, with non-depolarizing properties and an intermediate duration of action. The compounds disclosed in the above-mentioned patents comprise various mixtures of *cis* and *trans* isomers of undefined compositions.

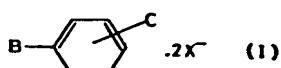
The four asymmetric centers present in each compound in all the above mentioned patents allow for sixteen possible stereoisomers. However, only ten stereoisomers can exist due to the symmetry of the 65 molecular structure; four *dL* pairs (one all *trans*, one all *cis*, two *cis, trans*) and two meso forms (one all *cis*, 65

one all *trans*). It is now recognized that the route of synthesis as well as the actual experimental conditions determines the *cis/trans* ratio and the stereoisomeric ratio. None of the issued patents addresses the question of the stereoisomers, hence they do not teach or even suggest ways for separating the different isomers. Moreover, the above mentioned patents do not teach or suggest that different potencies, durations 5 of action or side effects would exist for the different isomers in the mixtures.

We have discovered a way of providing the all *trans* (one dl pair, one meso form) and the all *cis* (one dl pair, one meso form) compounds. These diastereomers exhibit different neuromuscular blocking activities 10 in their potencies and/or durations of action. In the cat, the all *trans* compounds showed superior potencies, the difference in potencies was not as evident, but the durations of action of the all *trans* compounds were 15 markedly shorter (2-3 times) of those of the corresponding all *cis* compounds. The unexpected differences in duration were explained by measuring the hydrolysis rates by acetylcholinesterase *in vitro*. The rates of hydrolysis of the *cis* compounds were very slow compared to that of the corresponding *trans* form.

According to a first aspect of the present invention, there is provided a compound of formula (I):

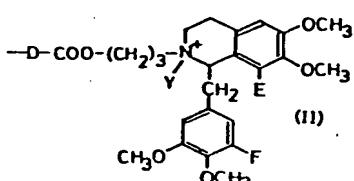
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wherein B and C are each a group of formula (II):

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where D is CH_2 , CH_2 or $\text{CH}=\text{CH}$; Y is a alkyl of 1 to 4 carbon atoms; E and F are H or OCH_3 ; X^- is an anion; and 30 the substituted benzyl and substituted propyl groups are in a *trans* relationship relative to each other in the nitrogen-containing ring.

Preferred compounds are those wherein C is *meta* or *para* to B. Y is conveniently methyl and D is preferably CH_2CH_2 or *trans* $\text{CH}=\text{CH}$. It is also preferred that X^- be a pharmaceutically acceptable anion.

Preferred compounds of the present invention include pharmaceutically acceptable salts of

35 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenedipropionate,
40 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenedipropionate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenedipropionate,
45 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenedipropionate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenedipropionate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
50 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenedipropionate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
55 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
60 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate,
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate and
bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate.

65 Especially preferred compounds are diiodide, dichloride or dimesylate salts. Compounds may advan-

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tageously be in the form of the *d*-, *l*- or *meso*-isomer or a mixture of two or three of the said isomers.

Since the activity of the compounds of the invention resides in the dication, the nature of the anion X^- is relatively unimportant. Other suitable pharmaceutically acceptable anions, however, include tosylate, bromide, sulphate, phosphate, hydrogen phosphate, acetate, benzenesulphonate, succinate, maleate, 5 naphthalenesulphonate and propionate.

It will be appreciated that the compounds of the invention can exist as an approximately 1:1 mixture of the racemic (dl) pair and the *meso*-isomer. This invention further provides means for obtaining the compounds of formula (I) when in the form of one of the aforesaid isomers substantially free of the other isomers, and mixtures of one of the isomers with one or both of the other isomers.

10 It is preferred that the compounds of the invention be provided in a form where the ratio of the *trans*, *trans* compound of the invention to the total of any corresponding *cis*, *cis* and *cis*, *trans* compounds present as impurities is at least 96.4.

Compounds of formula (I) may be useful as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration, e.g. intramuscular or intravenous

15 administration in solution. The compounds of the present invention shown in formula (I) may be administered to patients such as monkeys and man (humans) and other mammals to achieve a neuromuscular block. The dosage for each type of patient will vary because of the peculiarities of the species. However, a suitable intravenous amount or dosage of the compounds of formula (I) to obtain paralyses for monkeys and humans suitable for surgery would be 0.05 to 1.5 mg/kg of body weight, and 20 most preferably 0.1 to 1.0 mg/kg of body weight, the above being based on the weight of the dication which is the active ingredient.

The dosage for intramuscular administration is two to four times the intravenous dose. The compounds of this invention would normally be readministered about every 5 to 45 minutes, depending on whether the activity of the compound is of short or intermediate duration, preferably every 5 to 30 minutes, after initial 25 administration or given as a continuous infusion depending upon the length of time a muscular block is desired, and as determined by the anaesthetists and surgeon in charge of the patient. The compounds of this invention are reversible using conventional anticholinesterase agents such as neostigmine and edrophonium and appear to avoid the side effects associated with the depolarizing agents.

The compounds of formula (I) therefore appear to be useful for producing a short or intermediate duration 30 neuromuscular blockade, and the present invention enables the provision of a method of producing such blockade in mammals, eg man, or monkeys by intravenously injecting a dose of 0.05 to 1.5 mg/kg to the mammal.

According to a second aspect of the invention, there is provided a pharmaceutical preparation suitable for parenteral administration comprising an effective neuromuscular blocking amount of a compound in 35 accordance with the first aspect and a pharmaceutically acceptable liquid carrier.

The preparation may be an aqueous or non-aqueous solution or emulsion in a pharmaceutically acceptable liquid or mixture of liquids, which may contain bacteriostatic agents, antioxidants, buffers, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such a preparation may be presented in unit dosage form such as an ampoule or a disposable injection device, or in multidose 40 form such as a bottle from which the appropriate dose may be withdrawn; all such preparations should be sterile.

The compounds of this invention may be presented as a powder, eg as a unit dose in a sealed vial to which sterile water or other pharmaceutically acceptable sterile liquid vehicle may be added, preferably by aseptic techniques.

45 A suitable unit dose to obtain a neuromuscular block for mammals, eg humans or monkeys is about 1.0 mg to 300 mg and most preferably 5.0 to 200 mg.

The compounds of this invention if desired may be administered in conjunction with other non-depolarizing agents such as listed above.

Thus a suitable pharmaceutical preparation for administration to humans will preferably contain 1.0 to 300 50 mg of the compounds of formula (I) of this invention in solution.

A simple and preferred preparation is a sterile aqueous solution of the compound of formula (I), which may be prepared by simply dissolving the compound into previously sterilized pure water, ie. pyrogen free water under aseptic conditions and sterilizing the solution.

The compound of formula (I) may also be administered as an infusion of a dextrose solution or a saline 55 solution, eg. Ringers' solution.

The compounds may also be administered in other solvents such as alcohol, polyethylene glycol and dimethylsulphoxide. They may also be administered intramuscularly as a suspension.

The compounds of this invention provide the same percentage neuromuscular block at unexpectedly lower doses than the previously described *cis/trans* mixtures. Consequently, the possibility of side effects 60 such as abnormal lowering of blood pressure, histamine release, tachycardia, etc. is substantially reduced. Furthermore, our invention provides means to prepare mixtures of specified isomeric composition.

According to a third aspect of the present invention, there is provided a method for the preparation of a compound in accordance with the first aspect of the invention which comprises the separation of the *trans* isomer of a corresponding *N*-(3-hydroxypropyl)- or *N*-(3-halopropyl)tetrahydroisoquinolinium salt from a 65 mixture of the *cis* and *trans* isomers, and reacting the product with an appropriate phenylenedicarboxylic

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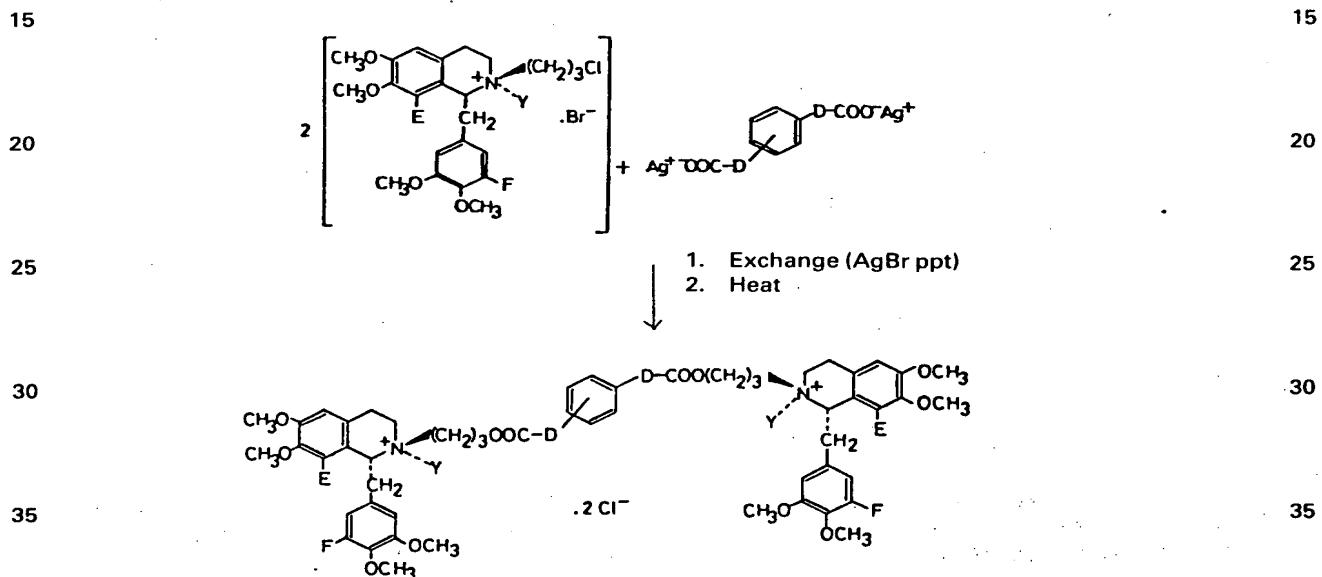
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acid or a reactive derivative thereof, and, if desired, converting the product to an alternative salt. In particular, the compounds of formula (I) may be prepared by the following methods.

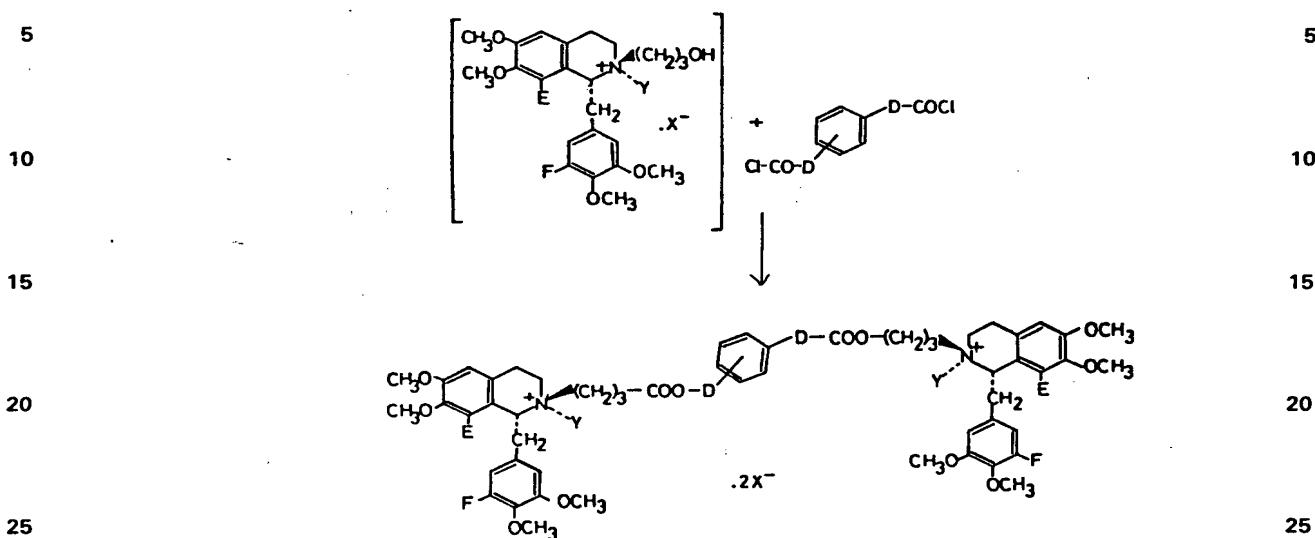
5 *Method 1*

Benzyltetrahydroisoquinolines are prepared in the customary fashion from homoveratrylamine or mescaline and homoveratric acid or 3,4,5-trimethoxyphenylacetic acid via the Bischler-Napieralski reaction and reduction/alkylation.

The tertiary benzyltetrahydroisoquinoline is quaternized with an appropriate 1,3-dihalopropane, such as 1-bromo-3-chloropropane 3-chloro-1-iodopropane or 3-bromo-1-iodopropane. From the resulting *N*-alkyl-*N*-3-halopropyl-1-benzyltetrahydroisoquinolinium halide the *trans* isomer is separated and is boiled in water with the silver salt of the appropriate dicarboxylic acid, yielding silver halide and the benzyltetrahydroisoquinolinium salt of the acid. This salt reacts to the corresponding ester on heating, preferably at 90° to 140°C. For example, the generalized reaction is illustrated as follows:



The bis acid chloride is then esterified with, e.g., two moles of the appropriate quaternary salt containing a 3-hydroxypropyl chain. This is illustrated below where D, E, F, X and Y are as defined above.



To prepare the all *trans* bis quaternary salts, having enhanced potencies and greater freedom from side effects, requires the preparation of a *trans*-*N*-3-hydroxypropyl-*N*-alkyltetrahydroisoquinolinium salt with a total of 4-6 methoxy groups as described in formula (II) for coupling with the *meta* or *para*-phenylene dipropionic or diacrylic acids. *Trans* and *cis*-*N*-3-hydroxypropyl-5'-methoxylaudanosinium salts, for example, are diastereomers and theoretically separable by physical methods, e.g. crystallization. However, literature precedent suggests that this separation is difficult. For example Stenlake *et al.* [J.B. Stenlake, W.D. Williams, N.C. Dhar, and I.G. Marshall, Eur. J. Med. Chem. - Chimica Therapeutica, 9, 233 (1974)] reported the synthesis of mixtures of *trans* and *cis* *N*-ethylalaudanosinium iodides but were unable to separate them: "All attempts to separate the components of these mixtures by crystallization and chromatographic techniques were unsuccessful." We examined a variety of solvents for recrystallization of the *trans/cis* mixtures of *N*-3-hydroxypropyl-5'-methoxylaudanosinium iodide (*trans/cis* ratio about 2.5-2.7/1) afforded by quaternization of 5'-methoxylaudanosine with 3-hydroxypropyl iodide (See Table I). Most solvent categories were unsatisfactory. The mixture of *trans/cis* quaternary iodides was largely insoluble in ethers (tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane), esters (ethyl acetate, ethyl propionate), ketones (acetone, 2-butanone), and aromatic hydrocarbons (benzene, toluene, xylene). The insoluble residues showed little or no enrichment with *trans* isomer. Solvents useful for the separation included acetonitrile, some chlorinated hydrocarbons (e.g. dichloromethane, 1,2-dichloroethane), some alcohols (e.g. ethanol, 2-propanol), and water. Water is the most preferred solvent. Once enrichment of the *trans* isomer has been accomplished (e.g. by water recrystallization) further recrystallization from a variety of solvents (e.g. acetonitrile, ethanol) or trituration with acetone suffices to raise the *trans* content to ~98% or higher.

TABLE I

Separation of *Trans/Cis N-3-Hydroxypropyl-5'-methoxylaudanosinium Iodide*
A sample of *trans/cis* iodide (2.6/1 by HPLC) was heated in a solvent, filtered hot, cooled to 25° and filtered
5 again.

		Trans/cis Ratio (Recovery)			
	Solvent	Concentration (ml/g)	Insoluble Salts	Recrystallized Salts	
10	tetrahydrofuran	10	2.7/1 (90%)	NP	
	1,4-dioxane	10	2.8/1 (71%)	NP	
	1,2-dimethoxyethane	10	2.6/1 (83%)	NP	
15	acetone	10	2.7/1 (81%)	1.1/1 (1%)	15
	2-butanone	10	3.4/1 (82%)	1/1.1 (8%)	
20	ethyl propionate	10	2.7/1 (96%)	NP	
	ethyl acetate	10	2.6/1 (88%)	NP	20
25	acetonitrile	10	CS	1/2.6 (28%)	
	dichloromethane	2	1/15.8 (21%)		
	chloroform	2	CS	1/6.2 (2%)	25
	carbon tetrachloride	10	2.6/1 (96%)	NP	
30	1,2-dichloroethane	5	1/1.2 (30%)	4/1 (58%)	
	nitromethane	2	CS	1/1 (30%)	
	nitroethane	2	CS	2.3/1 (89%)	30
35	benzene	10	2.7/1 (~100%)	NP	
	toluene	10	2.7/1 (~100%)	NP	
	xylene	10	2.5/1 (~100%)	NP	
40	methanol	2	CS	6.8/1 (9%)	35
	ethanol	5	9.8/1 (27%)	1.9/1 (58%)	
	2-propanol	5	12.7/1 (38%)	1.5/1 (25%)	
	2-methoxyethanol	2	CS	2.8/1 (31%)	
45	formamide	2	CS	NP	40
	N,N-dimethylformamide	2	CS	NP	
	N-ethylacetamide	2	CS	2.6/1 (96%)	
50	Dimethyl sulfoxide	2	CS	NP	45
	Hexamethylphosphoramide	2	CS	NP	
Water		6.74	CS	1/5.17 (31%)	

50 Abbreviations: NP = No Precipitate, CS = Complete Solution

In another approach to the separation of *trans/cis* quaternary salt mixtures the iodide was first changed to a different anion. The mixture of iodides was converted to the corresponding chlorides by standard methods (anion exchange chromatography, metathesis with silver chloride, and metathesis with HCl gas) and a variety of solvents was examined, for separating the isomers (See Table II). Again, most solvents were unsatisfactory. Among ethers only 1,4-dioxane was selective. Ketones, esters, and aromatic hydrocarbons were ineffective. Nitroalkanes (nitromethane, nitroethane), acetonitrile, some alcohols (especially ethanol and 2-propanol), some chlorinated hydrocarbons (e.g. dichloromethane, 1,2-dichloroethane), dimethylsulfoxide, hexamethylphosphoramide, and N-substituted amides are useful solvents for obtaining the quaternary chloride enriched in the *trans* isomer. N-substituted amides (e.g. *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-formylpiperidine, *N*-formylmorpholine, *N*-methylformamide, *N*-methylacetamide, and *N*-ethylacetamide) are preferred solvents for the *trans/cis* separation. These amides may be used as recrystallization solvents or solvents for slurring enriched *trans* mixtures to increase further the *trans* isomer content.

TABLE II

Separation of *Trans/Cis N-3-Hydroxypropyl-5'-methoxylaudanosinium Chloride*
A sample of *trans/cis* chloride (2.9/1 by HPLC) was heated in a solvent, filtered hot, cooled to 25° and
5 filtered again.

		<i>Trans/cis Ratio (Recovery)</i>			
	Solvent	Concentration (ml/g)	Insoluble Salts	Recrystallized Salts	
10	tetrahydrofuran	10	2.6/1 (97%)	NP	10
	1,4-dioxane	10	132/1 (67%)	1/6 (24%)	
	1,2-dimethoxyethane	10	3.3/1 (96%)	NP	
15	acetone	10	3/1 (95%)	1/15 (2%)	15
	2-butanone	10	3.8/1 (97%)	1/11(3%)	
20	ethyl propionate	10	3.4/1 (99%)	NP	20
	ethyl acetate	10	3.3/1 (95%)	NP	
25	acetonitrile	10	100/1 (50%)	8.6/1 (6%)	25
	dichloromethane	10	101/1 (36%)	NP	
	chloroform	2	CS	NP	
	carbon tetrachloride	10	2.4/1 (99%)	NP	
30	1,2-dichloroethane	10	6/1 (76%)	1/2.9 (12%)	30
	nitromethane	5	CS	9.4/1 (56%)	
	nitroethane	10	80/1 (42%)	NP	
35	benzene	10	2.9/1 (99%)	NP	35
	toluene	10	3.1/1 (97%)	NP	
	xylene	10	2.4/1 (96%)	NP	
40	methanol	2	CS	NP	40
	ethanol	5	CS	17/1 (32%)	
	2-propanol	10	69/1 (30%)	9.1/1 (18%)	
	2-methoxyethanol				
45	formamide	2	CS	NP	45
	N,N-dimethylformamide	5	CS	6.7/1 (54%)	
	N-ethylacetamide	2	CS	8.8/1 (76%)	
50	Dimethyl sulfoxide	2	CS	18/1 (34%)	50
	Hexamethylphosphoramide	10	67/1 (40%)	NP	
Water		2	CS	NP	

50 Abbreviations: NP = No Precipitate, CS = Complete Solution

We have found that a particularly good separation of the *trans* isomer from the crude *cis/trans* mixture may be achieved by crystallization of the *N*-(3-hydroxypropyl)-*N*-methyl compound in the form of the iodide (*cis/trans* mixture) from water. The *cis*-isomer crystallizes preferentially. If required, the *trans*-enriched 55 filtrate may then be converted to the chloride, for example, by conventional anion exchange chromatography (e.g. using Dowex (Registered Trade Mark) 1-X8 chloride resin), and the solute recovered and slurried with dimethylformamide, when the *cis*-isomer preferentially dissolves, to leave a product containing only a trace of the *cis*-isomer.

We have also separated the *trans/cis* mixtures of *N*-3-hydroxypropyl*laudanosinium iodide*, of *N*-3-60 hydroxypropyl-8-methoxy*laudanosinium iodide*, and of *N*-3-hydroxypropyl-5',8-dimethoxy*laudanosinium iodide* by fractional crystallization.

It is desirable to use an intermediate having less than about 2% of the corresponding *cis*-isomer, in order to obtain a compound of formula (I) containing less than 4% of the *cis, cis* and *cis, trans* isomers. This degree of separation may be readily achieved using the processes outlined above.

Method 3

The appropriate 1-benzyltetrahydroisoquinoline prepared as described in Method 1 is quaternized with a 3-halopropanol such as 3-iodo, 3-chloro or 3-bromopropanol, and the *trans*-N-3-hydroxypropyl-1-benzyltetrahydroisoquinolinium salt is separated from the *cis* isomer as in Method 2.

5 The *trans* quaternary salt is coupled with the appropriate *meta*- or *para*-phenylenedipropionic acid by direct esterification. This method may also be used to couple the *trans*-quaternary salt with *meta* or *para*-phenylenediacrylic acid, but this reaction is slower. This operation is carried out in a suitable solvent (e.g. 1,2-dichloroethane) using an acid catalyst (e.g. *p*-toluenesulfonic acid). The reaction is driven toward completion of removal of water by use of drying agents (e.g. molecular sieves) or by azeotropic distillation.

10 Temperatures ranging from ambient to reflux may be employed. The final salt may be changed if desired by conventional anion exchange methods.

As previously stated, the compounds of formula (II) exist in three stereoisomeric forms, which may be separated from each other, if desired, by conventional methods. For example, the *meso*-isomer may be separated from the (*d,l*)-pair by fractional crystallization, or by preparative HPLC, and the *d*- and *l*-isomers 15 may be separated from each other by conversion to a salt of a single isomer of an optically active acid, followed by fractional crystallization. The product may then, if desired, be converted to an alternative salt by conventional anion exchange methods.

m- And *p*-phenylene diacrylic acids were prepared through Knoevenagel-Doebner condensation of isophthalic and terephthalic aldehydes with malonic acid. Terephthalic aldehyde (150 mM) and malonic acid 20 (180 mM) were mixed with pyridine (45 mL) and piperidine (1.5 mL). The mixture was heated on a steam bath (85°-95°) for 3 hours. The solution was then cooled at room temperature and distilled in vacuum to remove pyridine. The solid residue was washed in hot 2-propanol (70°) to remove residual pyridine. The product, *p*-phenylene diacrylic acid, was filtered and dried (mp >275°).

m-Phenylene diacrylic acid was prepared from isophthalaldehyde in exactly the same way. (mp >275°). 25 *m*- and *p*-phenylene dipropionic acids may be prepared using conventional processes by catalytic reduction, e.g. by reacting the corresponding phenylene diacrylic salt with hydrogen at 40 to 45 psi gauge pressure in the presence of 5% palladium on charcoal in water or dimethylformamide at room temperature to 55°C. For another method, see also Wagner & Zook, Synthetic Organic Chemistry© 1973, page 431, method 26.

30 The compounds of this invention may sometimes include water of hydration in various amounts and it is intended that this invention include such compounds containing water of hydration.

The following examples illustrate the invention but are not intended to be limiting. Temperatures are in degrees centigrade (uncorrected).

Primary analysis of the quaternary salt intermediates and the di-quaternary salt final products was 35 accomplished by high performance liquid chromatography (HPLC). Samples dissolved in methanol were injected onto a 25 cm × 4 mm silica gel column and eluted with an acidic methanol. Detection was based on absorbance at 280 nm; percentages were derived by integration of the areas under the curves. Nuclear magnetic resonance (NMR) spectra, combustion analyses, and Karl Fischer water analyses were obtained as needed to support structures. The stereochemistry of the *cis* and *trans* quaternary salts was confirmed by 40 x-ray crystallography of the *cis* iodide and the *trans* perchlorate of N-3-hydroxypropyl-5'-methoxylaudanosinium salts.

Example 1

N-3-hydroxypropyl-5'-methoxylaudanosinium iodide (Belgian patent 869,415 and West German Offenlegungsschrift No. 2833505) (50g, 73% *trans*) was dissolved in hot water, cooled and the solids were collected by filtration and dried in a vacuum oven (60°/3 hr) to yield 15.5g of solids analyzed by HPLC as 84% *cis*. The *trans* rich filtrate was applied to a 5 × 60 cm column packed with 110 g of Dowex 1-X8 chloride in water and eluted with 100 mL of water. The eluate was concentrated *in vacuo* to dryness. The residue was triturated with acetone, filtered and the solid was vacuum dried (60°/3 hr) to yield 28g of crude *trans* chloride. The 50 crude product was slurried in warm DMF, cooled and filtered. The solids were washed with cold DMF and hot acetone. The suspension was cooled, filtered and the solids washed with cold acetone and dried in a vacuum oven to yield 24.7g (80.5%) of *trans*-N-3-hydroxypropyl-5'-methoxylaudanosinium chloride, mp 209-211°. HPLC analysis showed this material to be 99.3% *trans*.

Example 2

Crude N-3-hydroxypropyl-5'-methoxylaudanosinium iodide (95.1% pure, 71.9% *trans* by HPLC, 412g) was recrystallized from water. The *trans* rich mother liquor was chromatographed on 1.00 kg of Dowex 1-X8 chloride. The eluate and washings were combined and concentrated *in vacuo* to a viscous oil. The residue was triturated with acetone, reduced in volume, cooled and filtered to yield 225g of crude *trans* chloride, 60 (97.7% *trans*). The crude product was slurried in warm DMF, cooled and filtered. The cake was washed with the DMF liquors and then with acetone. Finally the damp product was slurried in refluxing acetone, cooled, filtered, and dried to yield 206g (87.0%) of *trans*-N-3-hydroxypropyl-5'-methoxylaudanosinium chloride (99.9% *trans* of HPLC).

Example 3

N-3-hydroxypropyl-5'-methoxylaudanosinium iodide (50g, 72.5% *trans*, 26.7% *cis*) was dissolved in 337 mL of hot water. The solution was cooled to 25° for 3 hours. The mixture was filtered to yield 15.5g of *cis* iodide (83.8% *cis* - purified (>99% *cis*) by recrystallization from methanol). The filtrate was concentrated to dryness *in vacuo* to yield the *trans* iodide (95.6% *trans* by HPLC). The crude *trans* iodide was purified by recrystallization from dry acetonitrile (2.5 mL CH₃CN/g) to yield 99.6% *trans* iodide (71% recovery). In similar experiments 94.5% *trans* iodide gave 99.3% pure *trans* (67% recovery) and 97% *trans* gave 99.6% *trans* (86% recovery). *Trans* iodide was also purified by trituration with acetone (3 mL/g): 92.7% *trans* gave 97.7% *trans* (95% recovery). Ethanol (95%, 4 mL/g) could also be used as a recrystallization solvent: 97.7% *trans* gave 10 99.6% *trans* (61% recovery).

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Example 4

Trans-N-3-hydroxypropyl-5'-methoxylaudanosinium chloride (>99% *trans* by HPLC, 25.7g) was suspended in 300 mL of 1,2-dichloroethane. The mixture was cooled to ~70° and 1,3-phenylenedipropionyl chloride (6g, prepared by treatment of the corresponding acid with thionyl chloride) was added as a solution in dry 1,2-dichloroethane. The mixture was heated at reflux for 25 minutes; HPLC analysis indicated ~93% of product. The reaction mixture was cooled, stirred over potassium carbonate for 2.5 hours, filtered, and concentrated *in vacuo* to dryness. The crude product was dissolved in 300 mL of chloroform, and the solution was washed twice with 5% sodium chloride, twice with water, dried over anhydrous sodium sulphate, and concentrated *in vacuo* to give bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylenedipropionate dichloride as a white amorphous solid, 24g (87.4% based on a dihydrate).

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Example 5

25 *Trans-N*-3-hydroxypropyl-5'-methoxylaudanosinium chloride (>99% *trans* by HPLC, 124.6 g) was suspended dry 1,2-dichloroethane and a solution of 1,3-phenylenedipropionyl chloride, 32.7g, in 100 mL of 1,2-dichloroethane was added. The mixture was stirred at reflux for 45 minutes and cooled to 8°. Triethylamine, 22.9 g, was added. The mixture was concentrated *in vacuo*. The residue was dissolved in 1800 mL of chloroform. The chloroform solution was washed with 5% sodium chloride (2 × 450 mL), water (2 × 30 450 mL), dried over magnesium sulphate, clarified by treatment with charcoal, and concentrated *in vacuo* until foaming began. The residue was triturated with hexane and the mixture concentrated *in vacuo* again until foaming began. This process was repeated three times until a solid product was obtained. The slightly oily product was transferred to a mortar and triturated again with hexane to give a granular solid which was collected by filtration and dried (48 hours at 40°) to yield 127.5g (85.3%) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylenedipropionate dichloride.

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Example 6

40 *Trans-N*-3-hydroxypropyl-5'-methoxylaudanosinium chloride (>99% *trans* by HPLC), 5.06g, was coupled with *E,E*-1,4-phenylenediacryloyl chloride, 1.27g, by the procedure of Example 4 to yield 3.0g (50.7% as a dihydrate) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)-isoquinolinium]propyl} 1,4-phenylene-(*E,E*)-diacrylate dichloride.

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Example 7

45 1,3-Phenylenedipropionic acid (0.58 g), *trans-N*-3-hydroxypropyl-5'-methoxylaudanosinium chloride (3.2 g), *p*-toluenesulphonic acid monohydrate (1.75 g), and dichloroethane (60 mL) were combined in a 100 mL flask equipped with a sintered glass Soxhlet containing molecular sieve #4. The mixture was heated at reflux and was monitored by HPLC. After 35 hours the reaction mixture was cooled and washed with water (2 × 50 mL). The dichloroethane layer was stirred overnight with charcoal and magnesium sulphate (anhydrous). 50 The mixture was filtered and evaporated to dryness to give 3.11 g (84%) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylenedipropionate ditosylate.

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Example 8

55 *Trans-N*-3-hydroxypropyl-5'-methoxylaudanosinium chloride (5.00 g), 1,3-phenylenediacrylic acid (1.08 g), and *p*-toluenesulfonic acid monohydrate were combined in 1,2-dichloroethane and reacted by the procedure of Example 7. After 99 hours at reflux HPLC analysis showed 46.7% of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylene-(*E,E*)-diacrylate ditosylate.

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Example 9

60 *Trans-N*-3-hydroxypropyl-5'-methoxylaudanosinium chloride (>99% by HPLC), 5.07 g, was coupled with 1,4-phenylenedipropionyl chloride, 1.29 g, to yield 4.7 g (79.6% as dihydrate) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)-isoquinolinium]propyl} 1,4-phenylenedipropionate dichloride.

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Example 10

To a solution of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylenedipropionate diiodide tetrahydrate (0.65 g (prepared according to Example 4 using the pure *trans* iodide of Example 3) in acetonitrile (10 mL) was added to a 5 solution of silver methanesulphonate (0.22 g) in acetonitrile (10 mL). The mixture was stirred for 15 minutes and filtered to remove the precipitate of silver iodide. The filtrate was concentrated *in vacuo* to a brown oil which was taken up in denatured ethanol (SD3A) and filtered to remove excess silver methanesulphonate. The alcohol was evaporated *in vacuo*, and the residue was dissolved in acetonitrile and filtered. The 10 acetonitrile was evaporated *in vacuo* and the residue was dissolved in acetone. The acetone solution was filtered through Celite® (filter aid) and evaporated to dryness to yield 0.40 g (65%) of fluffy yellow crystals of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylenedipropionate dimethanesulphonate. Calcd. for C₆₂H₈₂N₂O₁₄.2CH₃O₃S.4H₂O: C, 57.29; H, 7.21; N, 2.08; S, 4.79. Found: C, 57.37; H, 7.10; N, 2.09; S, 4.79.

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Example 11

N-3-Hydroxypropyl-5'-methoxylaudanosinium iodide (10 g, 71% *trans*) was dissolved in methanol (100 mL). The solution was heated to reflux and hydrogen chloride gas bubbled through for 5 hours. The mixture was evaporated *in vacuo*, and the residue was stored overnight in a dessicator containing sodium hydroxide pellets. Acetone was added and evaporated *in vacuo*. Denatured alcohol (SD3A) was added and evaporated 20 *in vacuo* and the process repeated a second time. Upon the addition of acetone and seed crystals there was obtained 4 g of N-3-hydroxypropyl-5'-methoxylaudanosinium chloride (87% *trans* by HPLC). Slurrying in DMF gave the *trans* quaternary chloride (>98% *trans* by HPLC).

Example 12

Trans-N-3-hydroxypropyl-5'-methoxylaudanosinium chloride (>99% *trans* by HPLC), 5.06 g, was coupled with, *E,E*-1,3-phenylenediacryloyl chloride, 1.27 g, by the procedure of Example 4 to yield 6.0 g (100% as trihydrate) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,3-phenylene-(*E,E*)-diacrylate dichloride.

Example 13

5',8-Dimethoxylaudanosine (27.2 g) and 3-iodopropanol (27.2 g) were refluxed in dry acetone (150 mL) for 21 hr. High pressure liquid chromatography (HPLC) showed a *cis/trans* mixture of 1:4.3. The mixture was stripped to a gum and the excess iodopropanol was extracted with ether. The ether was decanted and the residual gum was dissolved in SD3A (300 mL) with slight warming. Cooling the alcoholic solution at 5° overnight gave a white crystalline solid which was filtered and dried. The yield was 29.2 g (73%) which was assayed as 89.9% of trans-N-3-hydroxypropyl-5',8-dimethoxylaudanosinium iodide and 10.1% of cis-N-3-hydroxypropyl-5',8-dimethoxylaudanosinium iodide. The mixture was recrystallized twice from SD3A (3.4 mL/g) to give 24.4 g (84% recovery) of a mixture assayed by HPLC as 97.8% *trans* and 2.2% *cis* iodides, mp 160-163°C. The mixture was dissolved in aqueous methanol (300 mL) and the solution was passed through a column packed with Dowex 1-X8 ion exchange resin (75 g, Cl⁻ form). The column was rinsed with methanol (150 mL) and the eluate and washings were combined, stripped to a white solid, triturated with acetone, filtered and dried. The yield was 18.1 g (87%) which was assayed by HPLC as 100% *trans*.

Calc. for C₂₆H₃₈NO₇Cl·2H₂O: C, 56.98; H, 7.72; N, 2.56; Cl, 6.47

45 Found: C, 56.97; H, 7.74; N, 2.52; Cl, 6.47

Example 14

50 Trans-N-3-hydroxypropyl-5',8-dimethoxylaudanosinium chloride (2.0 g) was coupled with 1,4-phenylenedipropionyl chloride (0.48 g) by the procedure of Example 4 to yield 700 mg (31% as a tetrahydrate) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*n*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl} 1,4-phenylenedipropionate dichloride.

Example 15

According to the procedure of Example 13, laudanosine (34 g) was quaternized with 3-iodopropanol (26 g) to give a 3:1 ratio of *trans/cis* N-3-hydroxypropyllaudanosinium iodides. Crystallization of the crude mixture gave the pure *trans* iodide which was converted to the corresponding pure *trans* chloride (>99% by HPLC). The yield for the quaternization was 87% and for the anion exchange was 82%.

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Example 16

Trans-N-3-hydroxypropyllaudanosinium chloride (3.6 g) was coupled with 1,4-phenylenedipropionyl chloride (0.96 g) by the procedure of Example 4 to yield 2.8 g (69% as a tetrahydrate) of bis{3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl} 1,4-phenylenedipropionate dichloride.

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Example 17

Trans-N-3-hydroxypropylaudanosinium chloride (5.0 g) was coupled with *E,E*-1,4-phenylenediacryloyl chloride (1.35 g) by the procedure of Example 4 to yield 2.3 g (40% as a tetrahydrate) of bis[3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl] 1,4-phenylene-(*E,E*-5 diacrylate dichloride.

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Pharmacological Activity

Cynomolgus monkeys were anaesthetized with thiopental (35-40 mg/kg) and diazepam (2-3 mg/kg) given intramuscularly. Anaesthesia was maintained with a mixture of halothane (0.25-0.75%), nitrous oxide (60%) 10 and oxygen (40%).

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Bis[3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl] 1,3-phenylenedipropionate dichloride (Compound A), bis[3-[1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl] 1,3-phenyl-enedipropionate diiodide (mixture of *cis* and *trans* isomers, Compound B) or bis[3-[*cis*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-15 trimethoxybenzyl)isoquinolinium]propyl] 1,3-phenylenedipropionate diiodide (Compound C) was administered intravenously. The common peroneal nerve was stimulated supramaximally with square wave pulses of 0.2 m sec duration at a rate of 0.15 Hz. Twitch contractions were recorded via the tendon of the tibialis anterior muscle.

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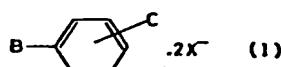
The ED₉₅, i.e. the dose required to produce 95% block of the twitch response, of compound A was 0.4-0.6 20 mg/kg and that of compound B was 0.5-1.0 mg/kg and that of compound C was 0.8-1.1 mg/kg (expressed as mg/kg cation).

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CLAIMS

25 1. A compound of formula (I);

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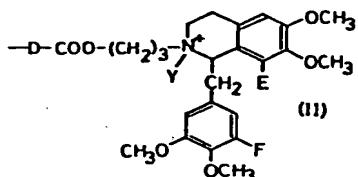
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wherein B and C are each a group of formula

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where D is CH₂CH₂ or CH=CH; Y is alkyl of 1 to 4 carbon atoms; E and F are H or OCH₃; X⁻ is an anion; and 45 the substituted benzyl and substituted propyl groups are in a *trans* relationship relative to each other in the nitrogen-containing ring.

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2. A compound according to claim 1 wherein C is *meta* or *para* to B.
3. A compound according to claim 1 or claim 2 where Y is methyl.
4. A compound according to any of claims 1 to 3 where D is CH₂CH₂.
5. A compound according to any of claims 1 to 3 where D is *trans* CH=CH.
6. A compound according to any of claims 1 to 5 wherein X⁻ is a pharmaceutically acceptable anion.
7. A compound according to claim 6 wherein X⁻ is iodide, mesylate, tosylate, bromide, chloride, sulphate, phosphate, hydrogen phosphate, acetate, benzenesulphonate, succinate, maleate, naphthalene sulphonate or propionate.

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55 8. A pharmaceutically acceptable salt of bis[3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl] 1,3-phenylenedipropionate.

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9. A pharmaceutically acceptable salt of bis[3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl] 1,4-phenylenediacrylate, bis[3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl]

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1,3-phenylenediacrylate, bis[3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl] 1,3-phenylenedipropionate, bis[3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl] 1,3-phenylenedipropionate,

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bis[3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl]-

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1,3-phenylenedipropionate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenedipropionate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl)-

5 1,4-phenylenedipropionate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]-propyl) 1,4-phenylenedipropionate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenedipropionate,

10 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,3-phenylenediacrylate,

15 15 propyl) 1,3-phenylenediacrylate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate,
 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4-dimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate, or

20 20 bis(3-[*trans*-1,2,3,4-tetrahydro-6,7,8-trimethoxy-*N*-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]propyl) 1,4-phenylenediacrylate.

10. A compound according to claim 8 or claim 9 which is a diiodide, dichloride or dimesylate.

11. A compound according to any preceding claim in the form of the *d*-, *l*- or *meso*-isomer or a mixture of two or three of the said isomers.

25 25 12. A pharmaceutical preparation suitable for parenteral administration comprising an effective neuromuscular blocking amount of a compound as defined in any of claims 1 to 11 and a pharmaceutically acceptable liquid carrier.

13. A preparation according to claim 12 in unit dosage form.

14. A preparation according to claim 13 where the amount of the compound is from 1 mg to 300 mg.

30 30 15. A preparation according to any of claims 12 to 14 in the form of a sterile aqueous solution of the compound of formula (I).

16. A method for the preparation of a compound of formula (I) as defined in claim 1 which comprises the separation of the *trans* isomer of a corresponding *N*-(3-hydroxypropyl)- or *N*-(3-halopropyl)tetrahydroisoquinolinium salt from a mixture of the *cis* and *trans* isomers, and reacting the product with an appropriate phenylenedicarboxylic acid or a reactive derivative thereof, and, if desired, converting the product to an alternative salt.

35 35 17. A method of preparing a compound according to claim 1 substantially as described in any one of Examples 4 to 10 and 14 to 17.

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